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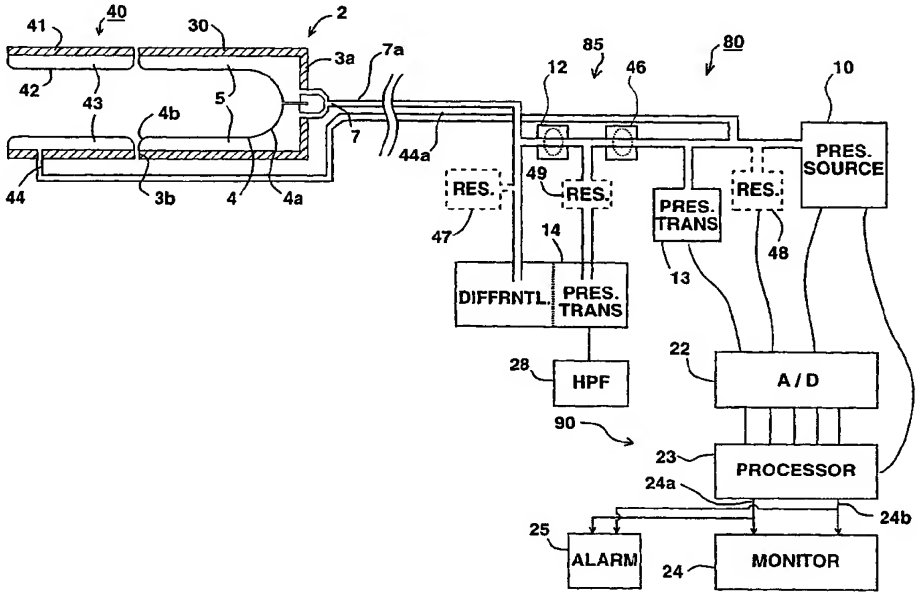

(57) Abstract: A method and apparatus for non-invasively determining the physiological condition of endothelial dysfunction (ED), hypopnea, or upper airway resistance syndrome (UARS) by: monitoring peripheral arterial tone using an external sensor; detecting a change in the peripheral arterial tone; and determining the physiological condition when a specific change in the peripheral arterial tone has been detected.

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DIAGNOSING MEDICAL CONDITIONS BY MONITORING PERIPHERAL ARTERIAL TONE

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to the method and apparatus of PCT Application No. PCT/IL97/00249, filed July 23, 1997, International Publication No. WO 98/04182, published 5 February 1998, hereby incorporated by reference as if fully set forth herein, for the non-invasive detection and monitoring of a physiological state or medical condition by monitoring peripheral arterial tone (PAT). More specifically, the present invention relates to monitoring changes in the peripheral arterial tone in reaction to such state or condition, particularly those related to cardiopulmonary distress and blood pressure in order to detect or monitor the physiological state or medical condition of the patient In several additional aspects over and above those described in PCT/IL97/00249.

Description of Related Art

As indicated above, PCT/IL97/00249 describes a method and apparatus for the detection and monitoring of various physiological states and medical conditions by detecting hemodynamic events in a body extremity of the patient. Several particular applications generally related to cardiopulmonary distress and blood pressure were described, namely: detecting myocardial ischemia; sleep staging; detecting sleep apnea syndrome; and continuously monitoring blood pressure.

The present application describes several additional applications, particularly in connection with the detection of additional sleep disordered breathing conditions and endothelial dysfunction (ED); the detection of coronary artery disease by mental stress tests; and other applications.

Sleep Disordered Breathing

In addition to the obstructive sleep apnea syndrome which results in frank cessations of breathing as described in PCT/IL97/00249

incorporated herein by reference, there are additional obstructive sleep disordered breathing conditions recognized in the medical literature. These additional conditions include hypopnea, and upper airway resistance syndrome (UARS), respectively. While these do not involve complete obstructions of the upper airway, they nevertheless are associated with important negative health consequences. In UARS frequent apneas and hypopneas do not actually occur, but the condition nevertheless results in frequent arousals and sleep fragmentation. UARS could also cause similar cardiac sequelae as OSAS, perhaps due to high levels of airway resistance. The diagnosis of UARS is much more difficult due to the condition's more subtle symptomatology. Guilleminault C, Stoohs R, Clark A, Cetel M and Maistros P, "A Cause of Excessive Daytime Sleepiness. The Upper Airway Resistance Syndrome.", Chest 104:781-787 (1993).

Detection of Endothelial Dysfunction (ED)

Endothelial dysfunction or "ED" is an important vascular disturbance related to risk factors for coronary artery disease. Following is a brief description of ED.

Vasoactive agents which influence the tonic state of arterial smooth muscle (VSM) can arise from within the single cell inner lining layer of the vessel known as the endothelium, or from sites external to this blood vessel wall layer. Vasoactive factors derived beyond the vessel wall include catecholamines from nerve endings serving VSM such as norepinephrine, or circulating factors such as vasopressin and epinephrine, and factors derived from circulating elements such as serotonin from circulating platelets. A group of vasoactive factors can also be derived from the endothelium. These factors can produce either an increase in the level of tonic activity of the blood vessels' VSM (vasoconstriction) or a decrease in the level of VSM tonic activity (vasodilation).

The term endothelial dysfunction refers to an impairment of the ability of endothelial cell layer to produce an appropriate vasodilatory response. An example of this is the vasodilatory response of coronary arteries

to acetylcholine (Ach), occurring in healthy vessels as opposed to a paradoxical vasoconstrictory response to Ach in vessels with ED. Ludmer PL, Selwyn AP, Shook TL, et al., "Paradoxical Vasoconstriction Induced by Acetylcholine in Atherosclerotic Coronary Arteries", N. Engl. J. Med. 315:1046 (1986).

Another example of endothelium mediated vasodilation which is important in regulating vascular tone is the vasodilatory response mediated by endothelium in response to increases in shear stress due to increased blood flow velocity within arteries. Kuo L, Davis MJ, Chilian WM, "Endothelium-Dependent Flow Induced Dilation of Isolated Coronary Arterioles", Am J Physiol 259; H1063 (1990). This mechanism can, for example, modulate neurogenically induced vasconstriction to better achieve homeostatic function.

Current diagnostic methods for detecting ED are not well suited for routine clinical use.

As an example, one current diagnostic method for detecting ED is a Brachial Artery Flow Response Duplex Test. This test involves inflating a blood pressure cuff above the patient's elbow to a predetermined pressure (e.g., 300 mm Hg) so as to stop blood flow to the arm below the cuff for a predetermined period of time (e.g., 4 minutes). A doppler flow rate probe and an echo doppler are used to measure relative changes in flow velocity and brachial artery caliber, respectively, prior to application and upon release of the occluding pressure. The results following release of the pressure cuff are compared to the pre occlusion state. If there is a sufficient increase in artery caliber then the patient is considered to have normal endothelial function.

The above described diagnostic method has several disadvantages. For example, it requires expensive apparatus and specialized personnel, and it suffers from a lack of accuracy and poor inter and intra-observer reproducibility. Of course, the method is also very uncomfortable to the subject since the pressure cuff is very tight around the subject's arm and blood flow must be stopped for a relatively long time, e.g., 4 minutes.

Mental Stress Testing

The mental arithmetic test is one of several methods which have been used to elicit mental stress for the purpose of diagnosing myocardial ischemia. Other tests include public speaking and the revealing of embarrassing personal details and the like. Irrespective of the mode of inducing the mental stress, the present state of the art methods for evaluating the cardiovascular effects of the stress requires a radio-nuclear method for measuring the resultant changes in cardiac function. Because of this dependency on highly expensive apparatus and skilled support staff, this mode of stress testing is of limited usefulness and accessibility.

Mental stress testing is of particular importance since it has been shown that cardiac patients, in whom mental stress induces myocardial ischemia, have significantly higher rates of subsequent fatal and non-fatal cardiac events and as such, mental stress testing has an important prognostic role in identifying particularly high risk patients. Jain D, Burg M, Soufer R, Zaret BL, "Prognostic Implications of Mental Stress Induced Silent Left Ventricular Dysfunction in Patients with Stable Angina Pectoris", AM J Cardiol. 73:31-35 (1995); and Jiang W, Babyak M, Krantz DS, Waugh RA, Coleman RE, Hanson MM et al., "Mental Stress Induced Myocardial Ischemia and Cardiac Events", JAMA 275:1651-1656 (1996). The induction of finger vasconstriction during mental stress testing in susceptible individuals may be related to sympathetic nervous system hyperresponsiveness, which has been linked to the pathogenesis and accelerated development of cardiovascular disease. Rozanski A, Blumenthal JA, and Kaplan J, "Impact of Psychological Factors on the Pathogenesis of Cardiovascular Disease and Implications for Therapy", Circulation 2192-2217 (1999).

Another very important aspect of detecting mental stress induced myocardial ischemia relates to so called "silent" myocardial ischemia, in which there are no pain symptoms and to "totally silent" ischemia, in which there is no pain symptoms and no ECG changes. It has been shown that a very large percentage, between 33% and 50% of heart patients may have these silent varieties of myocardial ischemia. (Kurata C. Tawarahara K, Sakata K, Taguchi

T, Fukumoto Y, Kobayashi A, et al., "Electrocardiographically and Symptomatically Silent Myocardial Ischemia During Exercise Testing", Japanese Circulation Journal 55;825-834, 1991); and Ishibashi M, Yasuda T, Tamaki N and Strauss HW, "Evaluation of Symptomatic vs. Silent Myocardial Ischemia Using the Ambulatory Left Ventricular Function Monitor (VEST)", Isr. J. Med Sci. 25:532-538 (1989).

Standard exercise testing with ECG could fail to diagnose such patients. The PAT due to its high sensitivity could facilitate an accurate diagnosis in such cases without having to rely on the costly and poorly available radio-nuclear tests.

OBJECTS AND SUMMARY OF THE PRESENT INVENTION

An object of the present invention is to provide a method and apparatus for non-invasively determining a number of physiological conditions particularly in connection with the detection of certain sleep disordered breathing conditions, ED, and coronary artery disease by mental stress tests.

Another object of the present invention is to adapt the method and apparatus of PCT/IL97/00249 for use in the above additional applications.

According to one aspect of the present invention, there is provided a method for non-invasively determining the physiological condition of endothelial dysfunction (ED), hypopnea, or upper airway resistance syndrome (UARS), sympathetic nervous system reactivity, or reactivity to a pharmalogical agent, in an individual, comprising: monitoring peripheral arterial tone of the individual using an external sensor; detecting a change in the peripheral arterial tone; and determining the physiological condition when a specific change in the peripheral arterial tone has been detected.

According to another aspect of the present invention, there is provided a method for non-invasively determining the existance of a coronary artery disease in an individual comprising: subjecting the individual to a mental stress test; monitoring peripheral arterial tone of the individual using an external sensor; detecting a change in the peripheral arterial tone; and determining the

existance of a coronary artery disease when a specific change in the peripheral arterial tone has been detected.

According to further features in a described preferred embodiment, the monitoring comprises viewing a peripheral arterial tone signal wave, the specific change is an early attenuation of the peripheral arterial tone signal wave during exercise and/or a slow amplitude increase of the peripheral arterial tone signal wave during recovery.

According to another aspect of the present invention, there is provided an apparatus for non-invasively determining the physiological condition of endothelial dysfunction (ED), hypopnea, or upper airway resistance syndrome (UARS) in an individual, comprising: a probe to be applied to a digit of the individual, the probe sensing the peripheral arterial tone of the digit and outputting signals indicative of the peripheral arterial tone; and a processor receiving the signals output from the probe and either: (a) providing an output indicating changes in the peripheral arterial tone from which the physiological condition can be determined; or (b) determining the physiological condition from changes in the peripheral arterial tone and providing an output indicating the physiological condition.

According to a still further aspect of the invention, there is provided apparatus for non-invasively determining stress-induced coronary artery disease in an individual comprising: a probe to be applied to a digit of the individual during a mental stress test of the individual, the probe sensing the peripheral arterial tone of the digit and outputting signals indicative of the peripheral arterial tone; and a processor receiving the signals output from the probe and either; (a) providing an output indicating changes in the peripheral arterial tone from which the presence of a stress-induced coronary artery disease can be determined; or (b) determining the presence of a stress-induced coronary artery disease from changes in the peripheral arterial tone and providing an output indicating the physiological state.

Further features and advantages of the invention will be apparent from the description below.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings, wherein:

Fig. 1 illustrates one form of apparatus, as described in PCT/IL97/00249 (Fig. 9), that may be used for the additional applications according to the present invention;

Fig. 2 illustrates another finger probe, including an optical sensor, which may be used in the apparatus of Fig. 1;

Fig. 3 is a table for comparing the results of detecting endothelial dysfunction using the present invention and a conventional brachial artery flow response duplex test;

Fig. 4 is a comparison of the waveform of peripheral arterial tone for a normal subject and a subject having endothelial dysfunction; and

Fig. 5 shows a comparison between a positive PAT response to mental stress shown as attenuation of the signal amplitude during the stress period (above), and a negative PAT response (below).

DESCRIPTION OF A PREFERRED EMBODIMENT

As illustrated in Fig. 1 (corresponding to Fig. 9 of PCT/IL97/00249), the finger probe 2 comprises a thimble-shaped end cap 30 and a pressure cuff 40 connected to a pneumatic system, generally designated 80, which is in turn connected to a processing system, generally designated 90. The pneumatic system 80 includes a pressure source 10 connected to a pneumatic tubing system, generally designated 85. The tubing system includes tubes 7a and 44a, which deliver the pressure from the pressure source to the finger probe 2, and electronic solenoid valves 12 and 46, which can be controlled by the processor 23 to be described later.

The pneumatic system 80 further includes a pressure transducer 13 for monitoring the pressure applied by source 10, and a differential pressure transducer 14 measuring the difference between the variable pressure in the finger probe chambers and the constant pressure existing between valves 12 and

46. Optionally, the pneumatic tubing 85 may be further provided with reservoirs 47, 48 and 49.

The processing system 90 includes an A/D converter 22, a processor 23, and a monitoring device, generally indicated as monitor 24 and alarm 25. The processing system is responsible for controlling the operation source 10 and solenoids of valves 12 and 46, and also processes the detected signals to provide a decipherable output.

In order to perform a diagnostic procedure, the valves 12 and 46 are first open and the chambers 5 and 43 of the finger probe are evacuated to allow the patient to insert a finger into the probe. Then, the pressure is raised to a pressure which is sufficient to unload the arterial walls and to prevent venous pooling. The pressure applied by source 10 is measured by a pressure transducer 13 upstream of valves 12 and 46. In the preferred embodiment, the pressure in the pneumatic compartments is automatically raised to 70 mm Hg.

At this point, valves 12 and 46 are closed, so that the pressure in the right chamber of pressure differential transducer 14 is kept constant. On the other hand, the pressure on the left chamber of transducer 14 varies depending on the pressure inside chamber 5 of the finger probe 2. Notably, for detection of peripheral vasoconstriction, no calibration of the inventive device is necessary, since the measurement is comparative with the patient's own baseline results observed during the test.

In order to obtain good results, relative immobilization of the hand being tested is desirable. During the various exercise stress tests this is usually achieved by holding the hand in a stable position and avoiding excess movement of the hand.

Changes in the volume of the subject's finger which are due to arterial blood pressure pulse waves produce an expansion or contraction of chamber 5, and a corresponding decrease or increase in the gas pressure within chamber 5. Chamber 5 is connected via its port 7 and tube 7a to the pneumatic tubing 85. However, since valve 12 is closed, the pressure changes affect only the left chamber of differential-pressure sensor 14. The differential pressure sensor 14

detects these pressure changes and provides an output corresponding to the pressure changes.

The A/D converter 22 shown in Fig. 1 receives the analog outputs of pressure transducers 13 and 14, and converts them into digital form before introducing them into a CPU processor 23. The processor 23 processes the measured finger volume (or optical density) changes to produce output 24a of the volume measurements, and/or an output 24b of the changes in the volume measurements with respect to time. Either one or both measurements can be displayed on the monitor 24.

If the displayed output 24 shows a change in the measured volume exceeding a predefined cut-off point, indicating peripheral vasoconstriction, this will be immediately seen by the observer viewing monitor 24. Optionally, an alarm 25 (e.g., audio or visual) may be actuated if this predetermined drop in measured volume occurs, to immediately alert the attendants.

The peak to trough amplitude of the signal is generally proportional to the arterial pulsatile volume changes, and will decrease upon peripheral vasoconstriction. Therefore, when the system of Fig. 1 is used for detecting peripheral vasoconstriction, the observer would be interested in relative changes of the amplitude of the trough to peak values, as opposed to the absolute values of the pressure. Accordingly, in the preferred embodiment, a high pass filter 28 is provided to filter the output of the transducer 14 and improve the signal to noise ration.

It is preferable that the finger probe include an annular pressure cuff 40 coaxial with and contiguous to the end cap 30, on the proximal (heart) side of the device. The main purpose of the pressure cuff is to extend the boundary of the constant pressure field beyond the borders of the sensing probe, so as to avoid edge effects. Chamber 43 of the pressure cuff is also filled with a pressurized gas via a port 44; however, solenoid valve 46 isolates conduit 44 from transducer 14. Cuff 40 thus extends the static pressure field for a distance in the proximal (heart) direction from the site of measurement of the finger volume changes accompanying blood pressure waves. The annular pressure cuff 40 acts as a tourniquet which, together with the pressure field produced in the

thimble-shaped end cap 30, prevents venous pooling in the distal end (particularly the most distal phalange) of the finger. It also substantially prevents uncontrolled venous back flow; and further, it partially unloads the wall tension of, but does not occlude, the arteries in the distal end of the finger when the finger is at heart level. While the pressure in the pressure cuff may differ from that in the sensing chambers 35, 36, it should not exceed it.

Fig. 2 illustrates an apparatus similar to that of Fig. 1 except that changes in the optical density are directly measured to provide a measurement of the changes in the finger accompanying the blood pressure waves. To facilitate understanding, the same reference numerals are used for corresponding parts as in Fig. 1.

Thus, in the apparatus illustrated in Fig. 2, chamber 5 is pressurized to a fixed predetermined value, as described above with respect to Fig. 1. In this case, however, the tubular diaphragm 4 defining chamber 5 is provided on one side with a light source 100, and on the opposite side with a light receiver 101, such that pulsatile blood volume changes in the finger received within the tubular diaphragm 4 will be detected as changes in optical density by the light receiver 101. This information is fed via conductors 102 to an amplifier circuit 103 where it is amplified and filtered, and then fed to the A/D converter 22 for processing by the processor 23 as described above.

In the arrangement illustrated in Fig. 2, the measurement site, namely the location of the light source 100 and light receiver 101, is considerably inward of the open end of the rigid casing 3 of the probe 2 which applies the static pressure field uniformly around the outer end of the finger, and therefore the annular pressure cuff (40, Fig. 1) need not be included for this purpose. However, if it is desired to locate the light source and light collector closer to the open end of the rigid casing of the probe 2, the annular pressure cuff (corresponding to pressure cuff 40 in Fig. 1, may also be used in the system illustrated in Fig. 2.

Further details of such apparatus, as well as various modifications thereof, and methods of using the apparatus for diagnosing various medical conditions, are described in the above-cited PCT/IL97/00249, International

Publication No. WO 98/04182 published 5 February 1998, and incorporated by reference as if fully set forth herein.

The finger probe 2, as described above and more fully in PCT/IL97/00249, could be used to house a pulse oximeter for measuring the oxygen saturation of blood. In such an application, conventional pulse-oximeter sensors could be included in the probe housing and would produce a better measurement of the oxygen saturation of the blood (SaO_2) because of the stable environment provided by the static pressure field.

As an alternative blood pressure calibration method to that described in PCT/IL97/00249, the generation of a compliance curve of the measured arterial blood vessels could be made by inducing and monitoring transmural pressure changes within the blood vessels. This could be done by changing the applied external pressure generated within the probe, and measuring the corresponding volumes and other volume correlated features of such arterial blood vessels and then plotting such measured values together with hydrostatic pressure changes. This would allow calibration to be performed without restricting a patient's movement. Transmural pressure changes may also be elicited by combined external pressure changes and induced hydrostatic pressure changes. The analysis of the compliance curve whether derived from external pressure changes alone, or from induced hydrostatic pressure changes alone, or from combined hydrostatic pressure changes and external pressure changes, is in all other respects identical to that already described.

While most of the description in PCT/IL97/00249 focuses on detecting myocardial ischemia, it describes other applications of the method and apparatus, including the use for monitoring various sleeping conditions of a subject, particularly the rapid eye movement (REM) sleep stage and sleep apnea syndrome (SAS) as well as nocturnal myocardial ischemia.

Sleep staging, in particular the determination of REM (Rapid Eye Movement) stage sleep, is a vital tool for diagnosing sleep disorders and numerous other conditions. During REM sleep, altered control of breathing

occurs with greatly reduced chemosensitivity resulting in highly irregular breathing patterns and the greatest declines in blood oxygen saturation.

Changes in REM latency have been reported in a plethora of affective illnesses including endogenous depression, schizophrenia, anxiety disorders, obsessive-compulsive disorders, eating disorders as well as in narcolepsy, alcoholism, Alzheimer's disease and impotence. REM latency is important not only in the diagnosis of these conditions but also in therapy and follow up since it is a sensitive indicator of the patient's condition.

There was a robust association between REM stage sleep and attenuation of the PAT signal. This attenuation was of a substantial magnitude compared to the prior non REM period. Three representative examples showing the time-course of the PAT signal and sleep hypnograms were shown in Fig. 21 of PCT/IL97/00249. It is important to note that the attenuation of the PAT amplitude was not triggered by REM sleep, but appeared to be related to an ongoing cycle that was synchronized with the sleep stages cycle in such a way that the nadirs of this cycle coincided with REM sleep.

The current state of the art method for identifying REM stage sleep is polysomnography which requires costly apparatus, considerable patient instrumentation and specialized staff. One simplified REM detector is the "night cap" disclosed in USA Patent No. 4,836,219 to Hobson et al. which relies on two channels of information to detect REM sleep; body movements and eye movements. However, this method requires substantial instrumentation which may be uncomfortable for the patient and detrimental to sleep. Another patented device (USA Patent No. 5,280,791 to Lavie) employs a heart rate variability method. However, this method requires demanding signal analysis, and may not be as reliable as the PAT method.

REM detection with the PAT could be an extremely useful adjunct to existing ambulatory monitoring systems, since it yields important information with a minimum of patient instrumentation in a highly cost effective manner. It could be used to provide intensive, long term, follow up in the patient's own home, which would be a logistic impossibility in the sleep lab setting. It could be readily used in combination with oxygen saturation monitoring and

ambulatory apnea screening function already described for PAT. It eliminates the need for subjective operator evaluation of sleep studies and the dependency on the specialized and expensive instruments needed for laboratory based sleep staging, such as EEG, EOG and EMG measurements.

DETAILED DESCRIPTION OF ADDITIONAL APPLICATIONS

Operation for Detecting Endothelial Dysfunction

In addition to the many applications described in PCT/IL97/00249, the peripheral arterial tone, or "PAT", was found to be an accurate detector of endothelial dysfunction (as demonstrated in the table in Fig. 3), when a characteristic response pattern was observed during a standardized exercise test procedure as shown in Fig. 4. The normal subject shows no decrease in amplitude of the PAT signal as the exercise progresses, whereas the ED subject shows a clear decline in the signal. In that study out of 23 subjects deemed negative for ED by the brachial artery duplex test (BAD), 20 were also found by the PAT to be negative responders. Of eight patients responding positively to the BAD test, 7 also had a positive PAT response. Thus, a high degree of agreement (87% accuracy) was shown between the PAT and the BAD test.

It may be possible to test for ED by applying the PAT sensor to the fingers distal to the occlusion site before, during and after the four (4) minute brachial artery occlusion procedure. The degree of increased pulsatile blood volume changes following release of the occlusion (relative to the pre-occlusion level) could be measured with the PAT, and depending on the extent of the change, a diagnosis of ED could or could not be made.

It may also be possible to use the PAT sensor itself to stop blood flow to the finger for a predetermined period of time instead of stopping blood flow to the arm as in the brachial artery duplex test already described. Following removal of the finger blood flow occlusion, it is possible to record the response in finger pulsatile volume using the PAT sensor in its normal manner. In this way, the endothelium mediated response and the vasodilatory response can

be tested without requiring the more extensive occlusion of blood flow to the hand and forearm as practiced today.

Mental Stress Testing

During mental stress testing, the inventors have discovered that some individuals exhibit vasoconstriction which may persist for the duration of the stress; other individuals show an early tendency to vasoconstrict which soon disappears; and still other individuals show little tendency to vasoconstrict.

When a group of subjects with coronary artery disease were subjected to mental stress testing, the inventors discovered that subjects with protracted vasoconstrictory responses had poorer cardiac performance based on concurrent nuclear cardiac imaging studies.

It was therefore determined that the probe of the present invention for measuring changes in arterial tone could be used in connection with conventional mental stress testing to predict coronary artery disease.

In a series of tests in which 18 men underwent mental stress testing with concurrent PAT and multigated radionucleotide ventriculography (MUGA) studies, it was found that eight out of nine patients with positive MUGA results also had positive PAT results, while six out of six negative MUGA responders were also negative by PAT. Two patients were equivocal. Of the remaining two cases, one patient had a positive MUGA response and a negative PAT response and one patient had a negative MUGA response and a positive PAT response. The overall accuracy of PAT compared to MUGA was 87%. Examples of a positive PAT response to mental stress shown as attenuation of the signal amplitude during the stress period (above, and a negative PAT response (below) are given in Fig. 5 where the beginning and end of the stress periods are indicated by 1 and 3, respectively.

Sleep Disordered Breathing

In 42 patients with Obstructive Sleep Apnea syndrome, the inventors found that profound, transient attenuation of PAT signal and tachycardia,

usually of a periodic nature, were clearly seen with each apneic event. Good agreement was found between standard total apnea-hypopnea scoring, 129.5 plus or minus 22.4 (Mean plus or minus SEM), and transient vasoconstriction and tachycardia events, 121.2 plus or minus 19.4 (R - .92, p is less than .0001).

Additional Applications

1) Autonomic nervous system activity or reactivity

Recently, information regarding the contributory role of autonomic nervous activity or reactivity in the pathogenesis of CAD has come to light. This suggests that autonomic nervous system activity or reactivity itself may be an important clinical parameter.

The ability of the PAT to detect reactive sympathetic nervous activity was demonstrated during induced myocardial ischemia as well as during mental stress testing. Sympathetic nervous system hyper-responsiveness has been linked to the pathogenesis and accelerated development of cardiovascular disease. Rozanski A, Blumenthal JA, and Kaplan J, "Impact of Psychological Factors on the Pathogenesis of Cardiovascular Disease and Implications for Therapy", Circulation 2192-2217 (1999).

Therefore, sympathetic nervous system hyperresponsivity may itself be an important clinical entity which the PAT is well suited to monitor. State of the art measurement of sympathetic nervous system activity is by way of direct intra-neural measurement of the peroneal nerve. This is an invasive procedure which is uncomfortable and carries the risk of injuring the patient.

2) Application of PAT in monitoring autonomic nervous system activity or reactivity;

The time-course of autonomic nervous system activity or reactivity can be monitored using the PAT. Such monitoring may incorporate the provocation of sympathetic nervous system reactivity via standardized tests known to the art, such as the cold pressor response, postural changes, inspiratory gasp, mental arithmetic, and so on. Normal limits of reactivity may be defined based on population studies.

The time-course of sympathetic nervous system changes during the passive tilting of patients can also be monitored using the PAT.

Additionally, the PAT signal could be monitored during pharmacological stress testing for diagnostic purposes or for pharmacologically eliciting sympathetic nervous responses, as well as for monitoring/evaluating the effects of pharmacological agents on the peripheral arterial tone.

3) Polygraphic evaluation and biofeedback treatment;

The monitoring of the PAT signal amplitude may also be used in the practice of polygraph testing, wherein the monitored parameter is related to sympathetic nervous system reactivity as it pertains to altered level of subject anxiety in response to examiner input.

The monitoring of the PAT signal amplitude may also be used in the practice of biofeedback, wherein the monitored parameter is related to sympathetic nervous system reactivity and the therapeutic goal is to train a patient to self regulate the level of sympathetic nervous system reactivity.

Although the invention has been described and shown in terms of preferred embodiments thereof and experimental set ups, it will be understood by those skilled in the art that changes in form and detail may be made therein without departing from the spirit and scope of the invention as defined in the appended claims.

WHAT IS CLAIMED IS:

1. A method for non-invasively determining the physiological condition of endothelial dysfunction (ED), hypopnea, upper airway resistance syndrome (UARS), sympathetic nervous system reactivity, or reactivity to a pharmalogical agent, in an individual, comprising:

monitoring peripheral arterial tone of the individual using an external sensor;

detecting a change in the peripheral arterial tone; and

determining said physiological condition when a specific change in the peripheral arterial tone has been detected.

2. A method for non-invasively determining the existance of a coronary artery disease in an individual comprising:

subjecting the individual to a mental stress test;

monitoring peripheral arterial tone of the individual using an external sensor;

detecting a change in the peripheral arterial tone; and

determining the existance of a coronary artery disease when a specific change in the peripheral arterial tone has been detected.

3. The method recited in Claim 1 or 2, wherein said monitoring comprises viewing a peripheral arterial tone signal wave.

4. The method recited in Claim 3, wherein said specific change is an early attenuation of the peripheral arterial tone signal wave during exercise and/or a slow amplitude increase of the peripheral arterial tone signal wave during recovery.

5. The method recited in Claim 1, wherein a stress test is performed to elicit hyperemia.

6. The method recited in Claim 1, wherein a stress test is performed to elicit autonomic nervous system activity or reactivity.

7. The method recited in Claim 1, wherein a pharmacological stress test is performed for diagnostic purposes.

8. The method recited in Claim 1, wherein a stress test is performed to pharmacologically elicit sympathetic nervous system reactivity.

9. The method recited in Claim 1, wherein the physiological condition is a patient's reaction to a pharmacological agent.

10. An apparatus for non-invasively determining the physiological condition of endothelial dysfunction (ED); sleep disordered breathing conditions of hypopnea, or upper airway resistance syndrome (UARS); autonomic nervous system activity or reactivity; or reactivity to a pharmacological agent, in an individual, comprising:

a probe to be applied to a digit of the individual, said probe sensing the peripheral arterial tone of the digit and outputting signals indicative of the peripheral arterial tone; and

a processor receiving the signals output from said probe and either: (a) providing an output indicating changes in the peripheral arterial tone from which said physiological condition can be determined; or (b) determining said physiological condition from changes in the peripheral arterial tone and providing an output indicating said physiological condition.

11. The apparatus recited in Claim 10, further comprising a device for determining whether the patient is in a sleep or awake state.

12. The apparatus recited in Claim 11, wherein the device for determining whether the patient is in the sleep or awake state is an actigraph.

13. The apparatus recited in Claim 10, wherein the output provided by said processor is a time-course of a peripheral arterial tone signal which is viewed so as to obtain biological information of the patient's level of autonomic nervous activity or reactivity.

14. The apparatus recited in Claim 10, wherein the output provided by said processor is a time-course of a peripheral arterial tone signal which is viewed so as to provide a patient with information regarding the patient's level of autonomic nervous activity or reactivity for therapeutic purpose of biofeedback treatment.

15. The apparatus recited in Claim 10, wherein the physiological state is that of the time-course of sympathetic nervous tone during a tilt test.

16. The apparatus recited in Claim 15, wherein the physiological state is that of variations of sympathetic nervous tone during a tilt test.

17. An apparatus for non-invasively determining stress-induced coronary artery disease in an individual during a mental stress test, comprising:

a probe to be applied to a digit of the individual, said probe sensing the peripheral arterial tone of the digit and outputting signals indicative of the peripheral arterial tone; and

a processor receiving the signals output from said probe and either: (a) providing an output indicating changes in the peripheral arterial tone from which the stress-induced coronary artery disease can be determined; or (b) determining the stress-induced coronary artery disease from changes in the peripheral arterial tone and providing an output indicating the physiological state.

18. The apparatus recited in Claim 10 or 17, further comprising a pulse oximeter for measuring oxygen saturation of arterial blood.

19. The apparatus recited in Claim 18, wherein said pulse oximeter is housed in said probe.

20. The apparatus according to Claim 10 or 17, wherein

said probe comprises a pressure applicator comprising:

a tubular socket for receiving a predetermined length of a distal end of a digit of the individual's body, including the extreme distal tip of the digit;

an end cup for receiving the extreme distal tip of the digit to prevent venous blood from pooling in the extreme distal tip;

at least one pressure cuff having a membrane configured to exert pressure on part of the digit preceding the extreme distal tip of the digit, to function as a venous tourniquet to prevent venous pooling and venous shock wave propagation in the digit;

a pressure source for applying a static pressure field around the distal end of the digit of the individual's body when received in said tubular socket, which static pressure is sufficient to substantially prevent venous pooling and propagation of venous shock waves in distal end of the digit and to partially unload but not occlude arteries therein; and

a measuring device for measuring changes in the distal end of the digit accompanying blood pressure waves;

and wherein said processor receives a signal output from said measuring

device and either: (a) provides an output indicating changes in peripheral arterial tone from which the physiological state can be determined; or (b) determines the physiological state from changes in the peripheral arterial tone and provides an output indicating the physiological state.

21. The apparatus recited in Claim 20, wherein said measuring device comprises a pulse oximeter for measuring oxygen saturation of arterial blood.

22. The apparatus recited in Claim 21, wherein said pulse oximeter is housed in said apparatus.

23. The apparatus recited in Claim 21, further comprising a device for determining whether the patient is in a sleep or awake state.

24. The apparatus recited in Claim 10, wherein the physiological state is that of the time-course of sympathetic nervous tone during a change in the body's posture.

25. A method for calibrating a blood pressure measuring instrument, the instrument comprising an end cap for receiving a patient's digit, the end cap having a pressure compartment configured to exert pressure on a distal part of the digit including the extreme tip of the digit, to prevent venous blood pooling a membrane configured to exert pressure on the digit preceding the distal part of the digit, to prevent venous blood pooling in the digit, and a sensor for detecting pulsatile volume changes of the arteries in the part of the digit contained within the instrument, said method comprising generating a compliance curve of measured arterial blood vessels by including and monitoring transmural pressure changes within the blood vessels by changing an applied external pressure generated within the instrument, and measuring corresponding volumes and other volume correlated features of the blood vessels and then plotting said volumes and features.

26. A method for calibrating a blood pressure measuring instrument, comprising the generation of a compliance curve of the measured arterial blood vessels by inducing and monitoring transmural pressure changing an applied external pressure generated within the instrument or by altering intra-vascular hydrostatic pressure, and measuring corresponding volumes and other volume

correlated features of such arterial blood vessels and then plotting such measured values and induced hydrostatic pressure changes.

27. A method for determining the effect of a pharmacological agent on peripheral arterial tone, comprising:

monitoring peripheral arterial tone using an external sensor;

detecting a change in the peripheral arterial tone; and

determining the effect of the pharmacological agent when a specific change in the peripheral arterial tone has been detected.

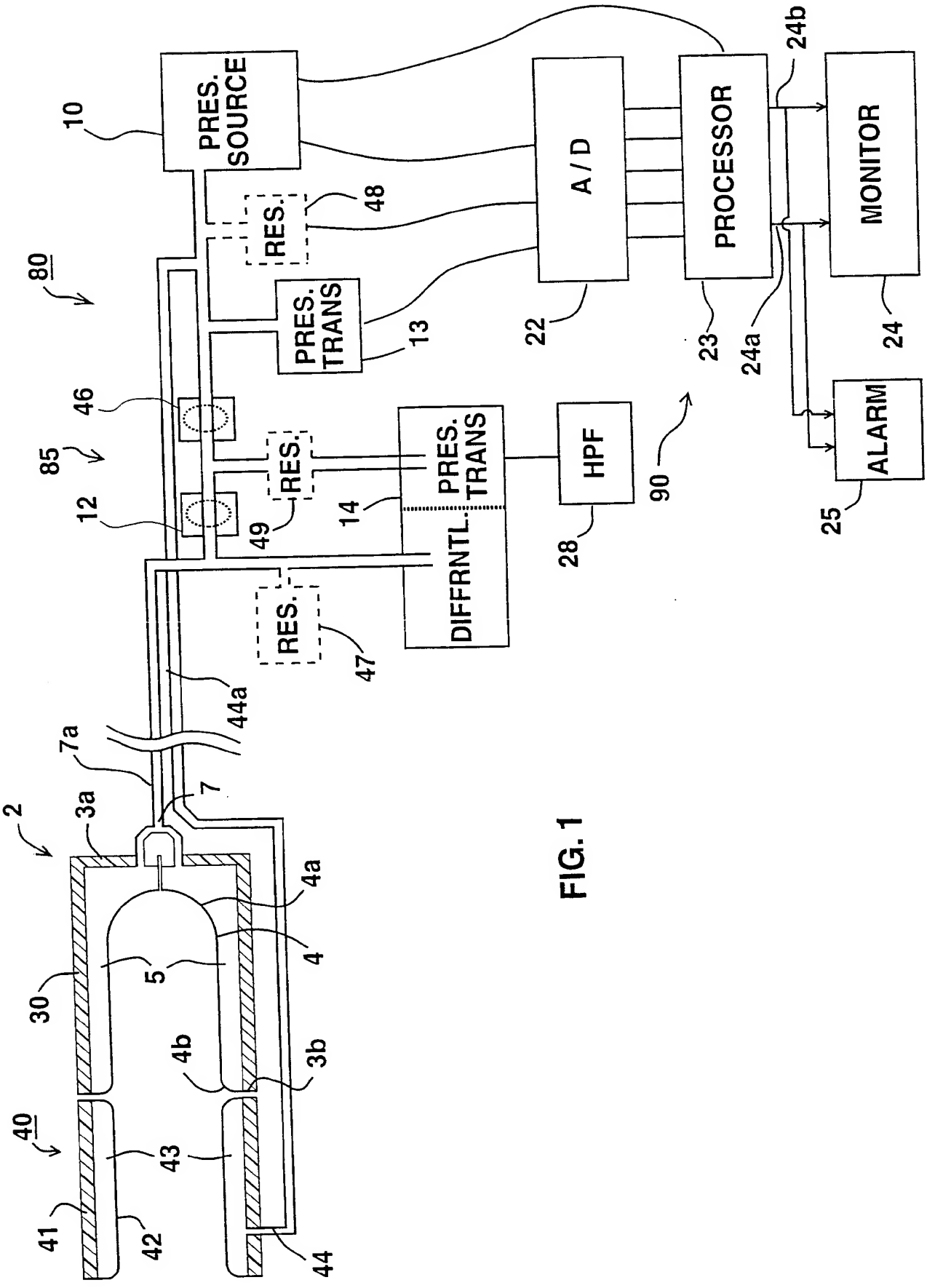

PRES. SOURCE
10
RES.
48
80
PRES. TRANS
13
A / D
22
PROCESSOR
23
24a
24b
MONITOR
24
46
85
RES.
49
12
14
PRES. TRANS
HPF
28
90
ALARM
25
RES.
47
DIFFRNTL.
44a
7a
7
3a
2
4a
4
5
30
4b
3b
40
43
41
42
44

FIG. 1

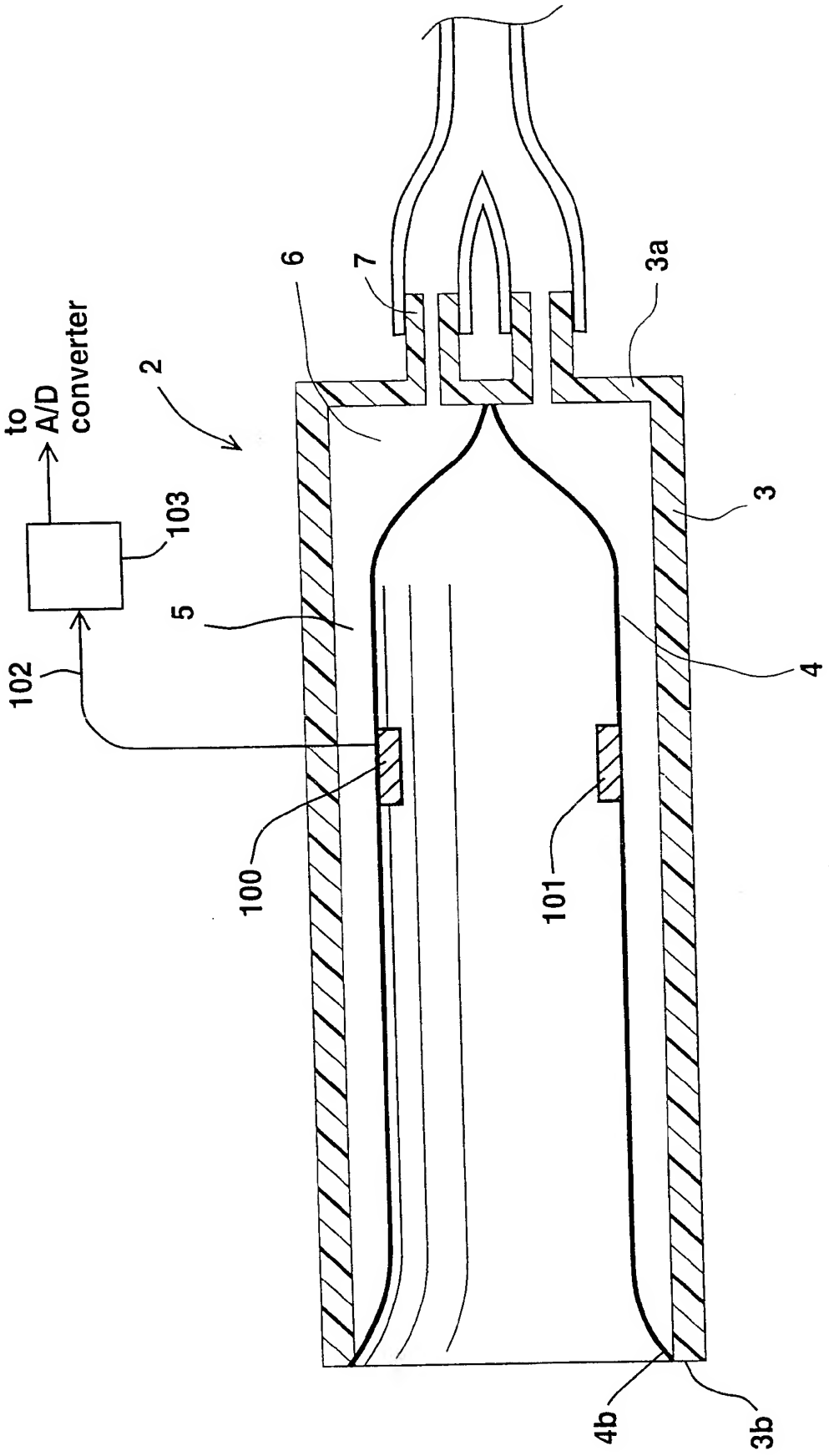
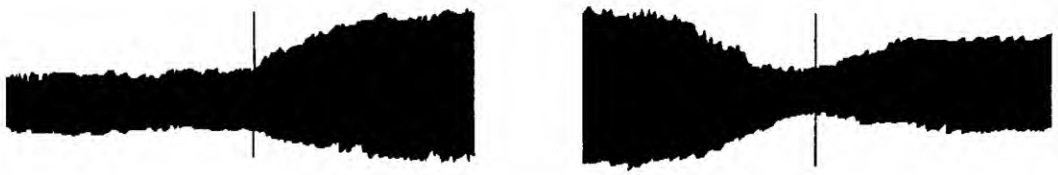


FIG. 2

	ED RISK		BRACHIAL ARTERY TEST		
	No (n=20)	Yes (n=21)	Negative (n=23)	Positive (n=8)	Borderline (n=10)
Pat Negative	**18**	6	20	0	4
Pat Positive	**2**	14	3	7	6
Pat Borderline	**0**	1	0	1	0
P	<.01		<.01		

Fig. 3



Normal Subject ED Subject

Fig. 4

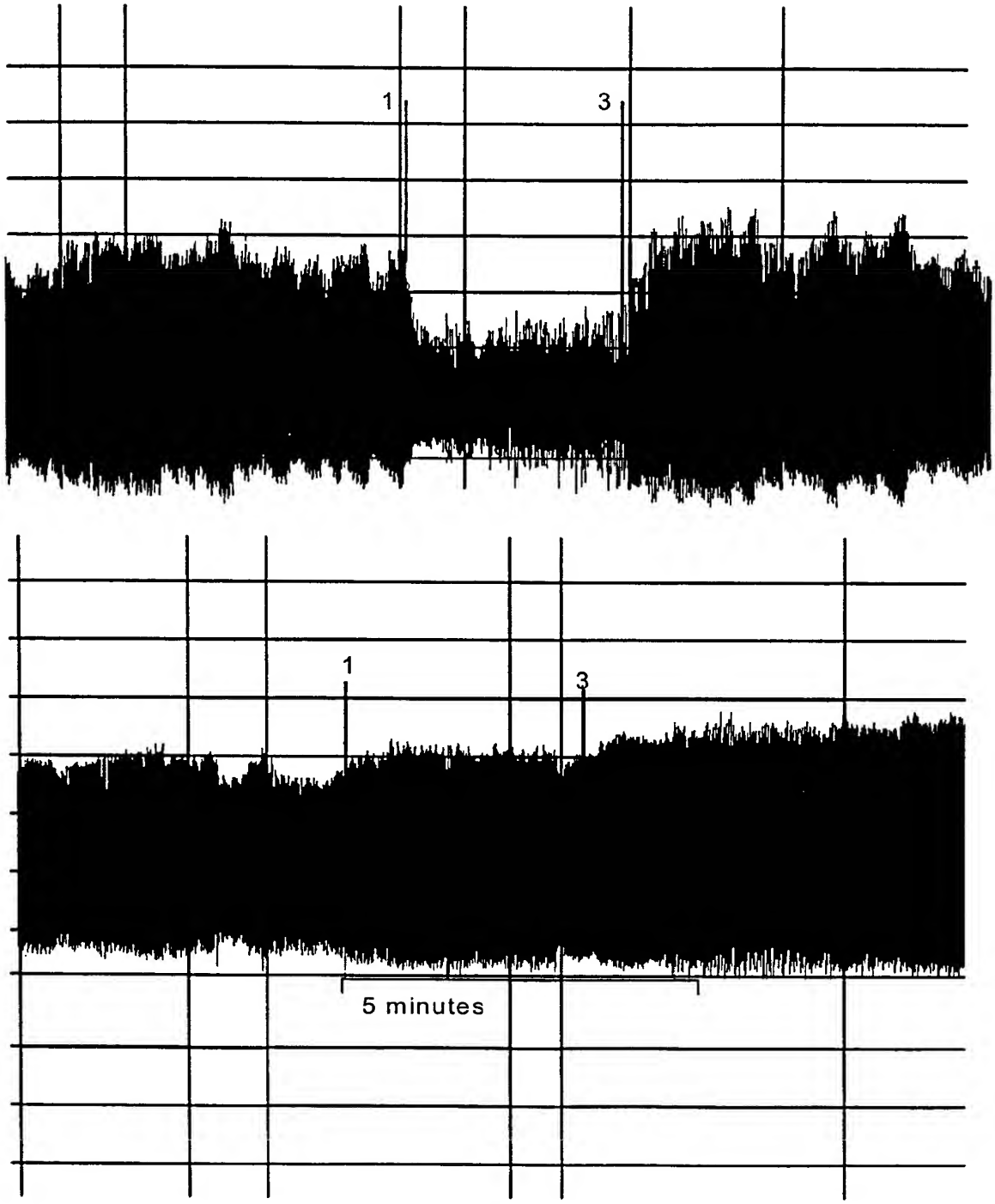


Fig. 5